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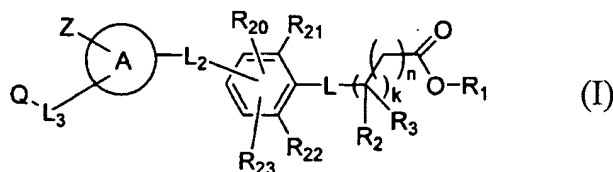
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(54) Title: SUBSTITUTED PHENYLALKANOIC ACIDS



(57) Abstract: The present invention relates to compounds and pharmaceutically acceptable salts of formula: (I) which are useful in the treatment of metabolic disorders related to insulin resistance or hyperglycemia. These compounds include inhibitors of protein tyrosine phosphatase (PTP-1B) that are useful in the treatment of diabetes and other PTP-1B mediated diseases, such as cancer, neurodegenerative diseases and the like. The compounds of the invention are also useful in pharmaceutical compositions and methods of treating the aforementioned conditions.

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A. CLASSIFICATION OF SUBJECT MATTER

C07C311/21 C07D213/55 C07C311/29 C07C69/612 A61K31/196
A61K31/4406 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DE 101 50 172 A1 (MORPHOCHEM AG) 30 April 2003 (2003-04-30) paragraph [0014]; claims; example 62	1,5-7, 9-13,19
X	WO 02/100341 A (WELLSTAT THERAPEUTICS CORPORATION; SHARMA, SHALINI; VON, BORSTEL, REID) 19 December 2002 (2002-12-19) page 17, line 16 - page 23, line 29; claims 92,153-160 example 52	1,5-7, 9-13,19

☒ Further documents are listed in the continuation of Box C

☒ See patent family annex

* Special categories of cited documents.

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

23 March 2006

Date of mailing of the international search report

07/04/2006

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	<p>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAJIMA, HISAO ET AL: "Preparation of phenylalkanoic acid derivatives as peroxisome proliferator-activated receptor controllers" XP002371578 retrieved from STN Database accession no. 1999:184126 abstract & WO 99/11255 A1 (ONO PHARMACEUTICAL CO., LTD., JAPAN) 11 March 1999 (1999-03-11)</p> <p>-----</p>	1,5-7, 9-13,19
X	<p>WO 00/64888 A (AVENTIS PHARMACEUTICALS PRODUCTS INC; JAYYOSI, ZAID; MCGEEHAN, GERARD,) 2 November 2000 (2000-11-02) claim 47: page 138, third compound in the right column, page 141, sixth compound in the right column, page 144, first compound in the right column, page 145, first column in the right column claims 53-87</p> <p>-----</p>	1,5-7, 9-13,19
X	<p>BOUCHAIN G ET AL: "Development of Potential Antitumor Agents. Synthesis and Biological Evaluation of a New Set of Sulfonamide Derivatives as Histone Deacetylase Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 46, 2003, pages 820-830, XP002278212 ISSN: 0022-2623 page 826, left-hand column, line 13 - line 27 page 828, right-hand column, line 24 - line 41 page 822, table 1, last compound in the right column</p> <p>-----</p>	1,5-7,9, 13,19
X	<p>LEONE-BAY A ET AL: "4-[4-[(2-HYDROXYBENZOYL)AMINOPHENYL]BUTYRI C ACID AS A NOVEL ORAL DELIVERY AGENT FOR RECOMBINANT HUMAN GROWTH HORMONE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, 21 June 1996 (1996-06-21), pages 2571-2578, XP002914793 ISSN: 0022-2623 table 1, compound 55; page 2572, left column, lines 15-27</p> <p>-----</p>	1,5-7,9, 13,19

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ASTLES, PETER C. ET AL: "Selective Endothelin A Receptor Antagonists. 4. Discovery and Structure-Activity Relationships of Stilbene Acid and Alcohol Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 15, 1998, pages 2745-2753, XP002371562 table 1, compounds 3 and 5 page 2751, line 46 - page 2752, line 6	1,5-7,9, 13,19
X	EP 0 612 743 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 31 August 1994 (1994-08-31) reference examples 1, 5, 6, 33-34, 36	1-7,13, 15,17,19
X	A. BAPNA ET AL.: "Polymer-assisted, multi-step solution phase synthesis and biological screening of histone deacetylase inhibitors" ORG. BIOMOL. CHEM., vol. 2, no. 4, 2004, pages 611-620, XP002371563 page 612, compounds 6, 8, 9 and 10 in combination with pages 615-616 for their preparation; table 2, synthesis intermediates of compounds 1a-1o and 1u-1x	1,5-7, 13,15, 17,19
X	R. LAVOIE ET AL.: "Design and Synthesis of a Novel Class of Histone Deacetylase Inhibitors" BIOORG. MED. CHEM., vol. 11, no. 21, 2001, pages 2847-2850, XP002371564 scheme 2, compounds 9 and 10; table 2, synthesis intermediates of 11c, 11h-11l	1,5-7, 13,15, 17,19
P,X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KITAMURA, YUSHI ET AL: "Hsp90 family protein inhibitor" XP002371590 retrieved from STN Database accession no. 2005:612072 abstract & WO 2005/063222 A1 (KYOWA HAKKO KOGYO CO., LTD., JAPAN) 14 July 2005 (2005-07-14)	1,5-7, 13,19
	-/-	

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DATABASE CROSSFIRE BEILSTEIN, Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371579 Database accession no. BRN 224657 abstract & BUU-HOI ET AL.: J. ORG. CHEM., vol. 18, 1953, page 1209, 1215, -----	15,17
X	DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371580 Database accession no. BRN 22403 abstract & HEILBRON ET AL.: J. CHEM. SOC., 1940, page 1279, 1283, -----	15,17
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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371584 Database accession no. BRN 3103769 abstract & R. H. ULOTH ET AL.: J. MED. CHEM., vol. 9, 1966, pages 88-97,</p>	15,17
X	<p>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371585 Database accession no. BRN 3409899 abstract & AINLEY; ROBINSON: J. CHEM. SOC., 1937, page 453, 455,</p>	15,17
X	<p>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371586 Database accession no. BRN 8423202 abstract & IGARASHI, SUSUMU ET AL.: CHEM. PHARM. BULL., vol. 47, no. 8, 1999, pages 1073-1080,</p>	15,17
X	<p>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371587 Database accession no. BRN 983606 abstract & H. GOTTHARDT: CHEM. BER., vol. 105, 1972, pages 196-202,</p>	15-17
X	<p>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371588 Database accession no. BRN 13930 abstract & GUSTAK: ARH. KEM., 24, 1952, page 15,</p> <p style="text-align: center;">----- -/-</p>	15-17

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371589 Database accession no. BRN 1307336 abstract & F. D. KING, D. R. M. WALTON: SYNTHESIS, 1976, pages 40-42, -----	15-17
P, X	WO 2004/092146 A (THE INSTITUTES FOR PHARMACEUTICAL DISCOVERY, LLC; VAN ZANDT, MICHAEL,) 28 October 2004 (2004-10-28) examples 3,5,6 -----	14
A	WO 99/58518 A (AMERICAN HOME PRODUCTS CORPORATION) 18 November 1999 (1999-11-18) page 1, line 6 - page 3, line 2; claims; examples -----	1-19

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 11-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 18

Claim 18 refers to compounds of the general formulae E-5 to E-9. All of them include a variable "W", which has not been defined. Also no definition could be found in the description. Claim 18 is thus not sufficiently clear to carry out a meaningful search. Consequently, no search report has been established for claim 18 (Art. 17(2)(a) and (b) PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 18
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; It is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
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INTERNATIONAL SEARCH REPORT

International application No

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